REMARKS WITH PRE-APPEAL BRIEF REQUEST FOR REVIEW

Claims 1, 2, 4-7, 11, 36 and 39 have been rejected under 35 U.S.C. 102(b) as being anticipated by Packard et al. (NEJM 2000 343:1148-1155).

Claims 1-2, 4-7, 10-11, 36 and 39 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over Packard et al. (NEJM 2000 343:1148-1155) and further in view of Rao et al. (US 2003/0120134).

Applicants respectfully traverse these rejections.

Reconsideration and withdrawal of these rejections is respectfully requested as they are based on mischaracterization and/or misunderstanding of the teachings of Packard et al.

Claim 1 recites a method for assessing risk of Coronary Vascular Disease (CVD) in a patient which comprises measuring levels of both Lipoprotein Associated Phospholipase A2 (Lp-PLA2) and C-reactive protein (CRP) or Low Density Lipoprotein Cholesterol (LDL) in the patient, analyzing a risk associated with the level of CRP or LDL and a risk associated with the level of Lp-PLA2, and combining the risks associated with the levels of CRP and Lp-PLA2 or the levels of LDL and Lp-PLA2 to assess the risk of CVD in the patient.

The Examiner's suggestion that Packard et al. teach the limitations of claim 1 including combining the risks is incorrect.

The Examiner's focus for these rejections is upon the title of Table 5 at page 1152 of Packard et al. "Multivariate Assessment of the Effect of Inflammatory Markers on the Risk of a Coronary Event." From this title, the Examiner suggests that "Packard specifically teach a multivariate assessment on the risk of a coronary event" and "as such, the models used the variables including CRP and Lp-PLA2 (i.e. combine the risks in the model)." See page 4, lines 21-22 of the Final Rejection

mailed May 26, 2010. Such focus improperly ignores the entire teachings of Packard et al., which make quite clear that individual markers were **not** combined to assess risk of CVD. Page 1150, 2nd column, 1st sentence of first full paragraph of Packard et al. states "The INDEPENDENCE of these variables as predictors of coronary events was assessed, as shown in Table 5…" The caption of Table 5 reads "Model 1 included the factors shown and tested the INDEPENDENCE of the factors to each other…".

The Examiner's suggestion that "…the models [of Packard et al.] which report risks necessarily use both LpPLA2 and CRP" is incorrect and appears to be based upon a misunderstanding of the models used by Packard. The models used by Packard **do not** report risks of CVD, only the independence of variables within the model to individually and independently assess risk of CVD. If the purpose of the models of Packard were to assess the risk of CVD in a patient using a combination of variables, each model as a whole would have a relative risk associated with it. No such information is provided in Packard et al.

Also incorrect are conclusions by the Examiner that "Packard teach that a model is used to calculate risks and the model uses variables including LpPLA2 and CRP (table 5). Thus the model uses a combination of risks." While Packard et al. uses the model to calculate the individual and independent risks of LpPLA2 and CRP, the model of Packard et al. does not use a combination of risks to assess CVD. The risks associated with LpPLA2 and CRP are the output of the model used by Packard. Unlike the present invention, the model used by Packard does not use this output of individual and independent risks for any further analyses. No assessment is made by Packard et al. whatsoever of the combination of the individual risks associated with LpPLA2 and CRP with a patient's risk of CVD.

Instead, Packard states "The importance of our findings regarding LpPLA2 is threefold," 1st : LpPLA2 is clinically significant and its activity is related to atherosclerotic disease; 2nd: "LpPLA2 appears to be a novel risk factor that is statistically INDEPENDENT of markers of inflammation or classic risk factors."; 3rd: inhibition of LpPLA2 has biological effects making it a potential therapeutic target. Nowhere does Packard conclude that the individual and independent risks associated with LpPLA2 and CRP can be combined to assess a patient's risk of CVD.

In accordance with MPEP 2123, a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art. Thus, while it is understood that terms in the claim such as "combine" and "assess" are to be given their broadest reasonable interpretation, the cited art should not be interpreted so broadly as to draw conclusions not drawn by the authors themselves or reasonably suggested to the skilled artisan.

Dr. Wolfert's Declaration submitted on April 17, 2009 should also be given proper consideration. Clear from Dr. Wolfert's Declaration is that he is very experienced in clinical diagnostics and statistical analysis utilized in developing diagnostic methods and products. Further, Dr. Wolfert's Declaration pertains directly to differences between Packard et al. and the instant claimed invention and is directly supportive of attorney argument regarding these differences rendering the instant claimed invention patentably distinguishable over Packard et al. Dr. Wolfert's understanding of the statistical models used by Packard et al. to determine how each marker is individually and independently associated with the risk of a cardiovascular event and the differences of such analysis as compared to the instant invention using combined individual

risks is based upon years of experience and education as well as known facts of the differences of various statistical models. Unlike the Examiner's opinion of what Packard et al. teaches, Dr. Wolfert's conclusion that Packard et al. determined how each marker individually affects the risk of a cardiovascular event is consistent with Packard's own conclusions.

Packard et al. does not teach combining the risks associated with the levels of CRP and Lp-PLA2 or the levels of LDL and Lp-PLA2 to assess the risk of CVD in the patient. Instead, Packard et al. clearly teaches that Lp-PLA2 is an **independent** [emphasis added] predictor of coronary heart disease, not part of a multivariate combined risk marker assessment on the risk of a coronary event. Specifically, in the "Statistical Analysis" section of the Methods on page 1149, Packard et al. states "We used multivariate conditional logistic-regression models to assess the **independent** [emphasis added] prognostic value of variables." Further, in the "Results" section at the first full paragraph in column 2 at page 1150 Packard states: "The **independence** [emphasis added] of these variables as predictors of coronary events was assessed, as shown in Table 5 and Figure 1." Finally in the last paragraph of the discussion Packard et al. concludes from their study that "C-reactive protein, fibrinogen and the white cell count are interrelated markers . . ." while Lp-PLA2 is concluded to be "a potential risk factor that may have a direct role in atherogenesis."

Accordingly, Packard, when read in its entirety by those skilled in the art is quite clear; multivariate assessment of variables (Lp-PLA2, CRP, etc.) was to determine **independence** of the variables, and not as "a multivariate assessment on the risk of a coronary event" or "a combination of [CRP and Lp-PLA2] risk factors" as suggested by the Examiner. Packard in no way

teaches **combining the risks associated with the levels of CRP and Lp-PLA2 or the levels of LDL and Lp-PLA2** as claimed.

Accordingly, since Packard does not teach all elements of the instant claimed invention, this reference cannot anticipate the claimed invention. See MPEP 2131.

Teachings of the secondary reference of Rao et al. fail to remedy deficiencies in Packard et al. as this reference is silent with respect to the claimed step of **combining the risks associated with the levels of CRP and Lp-PLA2 or the levels of LDL and Lp-PLA2** to assess the risk of CVD in the patient.

Thus, as the cited combination of references does not teach or suggest all claim limitations, the combination cannot render obvious the instant claimed invention. See MPEP 2143.

Reconsideration and withdrawal of these rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) is respectfully requested.

Respectfully submitted,

Kathleen A. Tyrrell
Reg. No. 38,350

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LICATA & TYRRELL P.C.
66 E. Main Street
Marlton, New Jersey 08053
ktyrrell@licataandtyrrell.com
(856) 810-1515